EXHIBIT J

Practitioner's Docket No. 051058-034000 (formerly NUCL 006/01-US) ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	PACHUK et al.	Confirmation No.:	3823
Application No.:	10/560,377	Group No.:	1648
Filed:	06/19/2006	Examiner:	PENG, Bo
For:	CONSERVED HBV AND HCV SEQUENCES USEFUL FOR GENE SILENCING		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Sir:

This is filed in response to the Non-Final Office Action mailed September 4, 2009 in the above-noted U.S. patent application. This is filed concurrently with a petition under 37 C.F.R. 1.182 to generate a separate Continuation-In-Part application from the parent PCT application PCT/US2005/046162 properly claiming the benefit of priority of US Provisional Application No. 60/638,294 filed December 22, 2004.

Amendments to the Specification:

Please replace the specification filed December 12, 2005 with the substitute specification submitted herewith – the replacement is a copy of parent PCT application PCT/US2005/046162 as filed. The substitute specification adds no new matter.

Please replace the first paragraph of the substitute specification submitted herewith with the following replacement paragraph:

CROSS REFERENCE TO RELATED ~~APPLICATION~~ APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. §371 of International Patent Application PCT/US2004/019229, filed June 10, 2004, which claims the priority of U.S. Provisional Application Serial No. 60/478,076, filed June 12, 2003, each of which is hereby incorporated by reference in its entirety.

Listing of the Claims:

The following listing of the claims is to replace all previous listings of the claims.

1-62. (Cancelled)

63. (Currently Amended) A method for inhibiting expression of a polynucleotide sequence of hepatitis B virus in an *in vivo* mammalian cell comprising administering to said cell a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

64. (Previously Presented) The method of claim 63, wherein at least two of said double-stranded RNA effector molecules are administered to the same mammalian cell.

65. (Currently Amended) The method of claim 64, wherein said at least two double-stranded RNA effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

66. (Previously Presented) The method of claim 65, wherein said administering is accomplished by providing one or more expression vectors capable of expressing in said mammalian cell said at least two double-stranded RNA effector molecules.

67. (Previously Presented) The method of claim 66, wherein said one or more expression vectors further comprise a promoter selected from an RNA polymerase I promoter, an RNA polymerase II promoter, a T7 polymerase promoter, an SP6 polymerase promoter, an RNA polymerase III promoter, a tRNA promoter, and a mitochondrial promoter, said promoter operably linked to a sequence encoding at least one of said double-stranded RNA effector molecules.

68-77. (Cancelled)

78. (Currently Amended) A composition for inhibiting the expression of a polynucleotide sequence of hepatitis B virus in an *in vivo* mammalian cell comprising a double-stranded RNA effector molecule, comprising an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:10; wherein U is substituted for T.

79. (Currently Amended) The composition of claim 78 comprising at least two double-stranded RNA effector molecules wherein said effector molecules comprise an at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within SEQ ID NO:3 and SEQ ID NO:10.

80-97. (Cancelled)

98. (New) The method of claim 63, wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

99. (New) The method of claim 98 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

100. (New) The composition of claim 78 wherein said double-stranded RNA effector molecule comprises a sequence selected from the group consisting of SEQ ID NOs 18-22 where U is substituted for T.

101. (New) The composition of claim 100 wherein expression of said double-stranded RNA effector molecule in an HBV cell culture transfection assay mediates at least 87% inhibition of HBsAg level relative to control lacking said effector molecule.

REMARKS

Claims 63, 65, 78, and 79 are amended herein to recite the limitation "at least 19 contiguous base pair nucleotide sequence *in a double-stranded conformation.*" Support for the amendment is found throughout the specification and particularly at page 30, lines 9-11; and page 34, lines 18-20.

New claims 98-101 are added herein. Support for the new claims is found, for example, in Example 1 of the specification, at pages 52-66. More specifically, support is found at pages 53-57 and in Tables 1, 4 and 6-8.

Specification- New Matter Rejections

Applicant cancels all subject matter considered by the Examiner in the Office Action issued September 4, 2009 to be "new matter" and provides herewith a copy of the PCT specification (from PCT/US04/019229) to serve as a substitute specification. Specifically, Applicants hereby cancel the amendments to the specification specified in the amendments filed a) with the National Phase entry application on December 12, 2005, and b) in the preliminary amendment filed June 19, 2006. Kindly enter the parent PCT specification submitted here as a substitute specification, and enter the amendment to the first paragraph specified in the "Amendments to the Specification" provided herein to recite the proper priority information.

A petition, marked-up and clean versions of the specification, and necessary fees under 37 C.F.R. §1.182 are also filed concurrently herewith requesting the generation of a CIP application of parent PCT/US04/019229 that claims the benefit of priority from and incorporates disclosure contained in that PCT and U.S. Provisional 60/638,294. Applicants note that all requirements for a National Phase entry under 35 U.S.C. §120 were fulfilled when the present application was filed, despite the application being termed a §371 National Phase application.

Rejections under 35 USC 102

1. Claims 63 and 78 are rejected under 35 USC 102(b) as being anticipated in view of US Patent No. 5,843,770 (the "Ill patent"). The rejection appears to be based on the interpretation that the claimed dsRNA can be in the form of single stranded DNA or RNA. The Office Action appears

to have misinterpreted the definition of "dsRNA" in the specification to include single-stranded nucleic acid molecules. This interpretation is simply not correct. The term "dsRNA" is defined in the PCT specification at page 19, lines 25-26, which recites "By 'dsRNA' is meant a nucleic acid containing a region of *two or more nucleotides that are in a double stranded conformation.*" Thus, the Office Action's interpretation that the dsRNA molecule as presently claimed encompasses single stranded nucleic acid molecules is not correct.

The Office Action has highlighted several phrases within the dsRNA definition including, for example, "dsRNA may include two different strands that have a region of complementarity to each other" and "a linear nucleic acid." These phrases are taken out of context by the Office Action to mean that the "dsRNA" encompasses single-stranded RNA. However, these phrases merely provide alternate dsRNA molecules, which by definition contain "two or more nucleotides that are in a double-stranded conformation," as discussed above. For example, taken in context, the reference to two different strands do **not** teach that the dsRNA **is** either one of these strands, but rather, when taken in context, teaches that a dsRNA can be made up of ("may include") two single strands with complementarity to each other. There is simply no basis for a conclusion that the term "dsRNA" somehow encompasses a single strand of RNA in a single stranded conformation. Even where the applicant is permitted to be their own lexicographer, they are not permitted to define something in a way repugnant to its usual meaning- that is, one cannot define "hot" as "cold" or "black" as "white." See *In re Hill*, 161 F.2d 367 (CCPA 1947). To interpret the language in the cited passage as somehow meaning that double stranded RNA equals single stranded RNA is similarly repugnant to the meaning of the term. A dsRNA can be formed from a single strand, but such a single strand would form a hairpin or otherwise have a double stranded region as required by the definition in the specification. Thus, the Office Action's interpretation that the term "dsRNA" encompasses single stranded molecules (i.e., molecules in a single-stranded conformation) is unfounded.

However, in the interest of advancing prosecution, Applicant has amended claims 63, and 78 to recite "at least 19 contiguous base pair nucleotide sequence *in a double-stranded conformation,*" to avoid any possibility of confusion.

With regard to the art rejections, Applicant notes that the art cited by the Examiner relates to single-stranded molecules. That is, molecules without double stranded character. The Ill reference is directed towards antisense constructs for inhibiting viral production. Antisense

molecules are known to those of skill in the art as being single-stranded nucleic acid molecules. The invention as presently claimed and as amended does not encompass single-stranded nucleic acid molecules. Therefore, the Ill reference does not teach all of the elements of the invention as presently claimed.

Applicant submits that the Ill reference does not anticipate the invention as presently claimed and respectfully requests withdrawal of the rejection under §102 over the Ill reference.

2. Claims 63 and 78 are rejected under 35 USC 102(b) as being anticipated by US Patent Application US20020155124 (now US Patent No. 6,680,059; the "Sallberg reference"). The Office Action cites the Sallberg reference as teaching a nucleic acid based antigen (SEQ ID NO: 14) comprising "a double-stranded RNA effector molecule comprising an at least 10 contiguous base pair nucleotide sequence." Applicant respectfully disagrees.

As discussed above, the Office Action has incorrectly determined that a "dsRNA" also encompasses single-stranded nucleic acid molecules. The claim amendments provided herein clarify this aspect by including the language "an at least 19 contiguous nucleic acid sequence *in a double stranded conformation.*" The Sallberg reference does not teach or suggest the use of an RNA molecule having at least 19 contiguous nucleotides in a *double-stranded* conformation. Thus, the Sallberg reference does not teach all of the elements of the claimed invention, and therefore does not anticipate the invention as presently claimed.

Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection based on the Sallberg reference.

Rejections under 35 USC 103

Claims 63-67, 78 and 79 are rejected as being obvious in view of Ill et al., Sallberg et al., and McCaffrey et al. Ill et al. is cited as teaching an expression plasmid encoding one or more antisense transcripts that can be used to inhibit viral production. Sallberg et al. is cited as teaching a nucleic acid-based antigen ("i.e., a vaccine") comprising a double-stranded effector molecule comprising an at least 19 contiguous base pair nucleotide sequence. McCaffrey et al., is cited as teaching RNAi to inhibit production of HBV replicative intermediates both in cell culture and in mice. The Office Action concludes that the combination of the three cited references teaches the invention as presently claimed. Applicant respectfully disagrees.

First, Applicants reiterate here the discussion above regarding the erroneous conclusion drawn in the Office Action that the term "dsRNA" encompasses single stranded RNA in a single-stranded conformation. This is simply incorrect. Amendment of the independent claims herein to further recite "an at least 19 contiguous base pair nucleotide sequence *in a double-stranded conformation*" is expected to remove any doubt in this regard.

Second, the Ill et al. and Sallberg et al. references do not teach double stranded RNA corresponding to any sequence, let alone double stranded RNA comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10, wherein U is substituted for T as required by the instant claims. Single-stranded antisense RNA (Ill et al.) and double-stranded DNA (Sallberg et al.) are not dsRNA molecules as defined in the instant specification.

The Office Action cites the Supreme Court's holding in *KSR v. Teleflex* to support a conclusion of obviousness, referring to the Court's statement:

> "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person or ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *KSR v. Teleflex,* 82 USPQ 2d 1385, 1390 (U.S. 2007)

The Office Action states that

> "in the present case, the prior art has provided a finite number of identified predictable potential solutions for the claimed method of inhibiting HBV in vivo using dsRNA molecules. Specifically, Ill teaches that an expression plasmid encoding one or more antisense transcripts (dsRNA effector molecule), which comprises the claimed SEQ ID NO: 10, can inhibit HBV production in mice. Sallberg teaches HBV nucleic acid-based antigen SEQ ID NO: 14, and its fragments, which comprises the claimed dsRNA effector molecule comprising SEQ ID NO: 3, can be used to inhibiting HBV in vivo. McCaffrey shows that each shRNA (dsRNA) targets the HBV pregenomic RNA, the mRNA for the core antigen and the polymerase, as well as the X region and its transcript, can inhibit HBV in cell culture. .... In turn, because the claimed oligonucleotides have the properties predicted by the prior art, it would have been obvious to make such dsRNA effector molecules for inhibiting HBV in vivo. Therefore the combined teachings of these references render the claimed invention obvious.

This conclusion is inappropriate for several reasons. First, because the Ill et al. and Sallberg et al. references do not relate to double-stranded RNAs, they do not set out or define a finite number of

identified predictable potential solutions to the problem of identifying double-stranded RNA inhibitors of HBV. Similarly, the possibility that a double-stranded DNA sequence can express an antigen that stimulates an immune response to HBV in no way relates to whether a dsRNA derived from the same sequence will inhibit viral expression or replication.

Second, while McCaffrey et al. may teach double stranded RNA in the context of HBV inhibition, the reference does not teach the use of a dsRNA comprising at least 19 contiguous base pair nucleotide sequence in a double-stranded conformation from within a sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 10 (see BLAST sequence alignments of the seven sequences taught by McCaffrey et al. with SEQ ID NOs 3 and 10 in attached **Exhibit 1**). That is, McCaffrey et al. does not teach targeting conserved region 3 as disclosed in the instant specification (SEQ ID NO: 3 corresponds to conserved region 3, and SEQ ID NO: 10 is a sub-sequence within SEQ ID NO: 3). Data provided in the instant specification show that five different dsRNAs (i.e., SEQ ID NOs 18-22) directed to conserved region 3 and its SEQ ID NO: 10 sub-region are effective in reducing HBsAg in culture by at least 87% relative to control (see, e.g.: Table 4, in which sequences 1907 (SEQ ID NO: 19; 90.9% inhibition), 1912 (SEQ ID NO: 20; 87.1% inhibition), 1943 (SEQ ID NO: 21; 87.4% inhibition), 1991 (SEQ ID NO: 22; 92.7% inhibition) are effective; Table 6, in which sequences 1737 (SEQ ID NO: 18, a sub-sequence of SEQ ID NO: 10; 91.9% inhibition) and 1907 (SEQ ID NO: 19, still showing 87.6% inhibition at approximately half the dose used in Table 4) are effective; Table 7, in which sequences 1737 (SEQ ID NO: 18; 89.8% inhibition at approximately 1/3 the dose used in Table 6; 1907 (SEQ ID NO: 19; 91.3% inhibition), and 1991 (SEQ ID NO: 22, ; 93.6% inhibition) are effective; and Table 8, in which sequence 1907 (SEQ ID NO: 19; 83.3% inhibition at a dose five times lower than in Table 4) is effective. Effectiveness of sequence 1907 (SEQ ID NO: 19) is demonstrated in the mouse model in vivo with data shown in Table 13.

Importantly, examination of the data presented in the McCaffrey et al. reference shows a wide range of efficacy with the sequences they did use, and that only two of the seven sequences tried in their experiments (HBVU6no.2 and, to a much lesser extent, HBVU6no.6) were particularly effective in inhibiting HBV surface antigen expression in vivo and in culture – that is, the reference demonstrates unpredictability with respect to the sequences that will or will not work as dsRNA inhibitors of HBV. The Office Action quotes McCaffrey et al.'s statement that "Each shRNA targets the pregenomic RNA serving as the template for HBV genomic replication as well

as the mRNA for the core antigen and the polymerase." However, this passage teaches what was targeted, not what worked. That is, not all of the sequences tried by McCaffrey et al. were effective. This is discussed further below.

Not only does McCaffrey et al. not support a predictable outcome, the reference does not provide a finite number of identified, predictable solutions to the problem of HBV inhibition in vivo – the broad range of different target sequences, combined with a range of potential different dsRNA sizes against a virus demonstrated to provide unpredictable inhibition with RNAi supports a different conclusion. Of particular note is that McCaffrey et al.'s sequence HBVU6no.1 did not very effectively reduce HBV expression, despite targeting sequence very close on the HBV transcripts to that sequence targeted more effectively by HBVU6no.2 (see, e.g., McCaffrey et al.'s Figures 1 and 2). Similarly, reference to the same figures shows that McCaffrey et al.'s HBVU6no.7 was not effective despite targeting sequence close to that targeted to a greater extent by HBVU6no.6. Again, this emphasizes that it is not predictable which part of *any* conserved sequence will be effective as a dsRNA. If the prior art does not support the predictable ability to target HBV using dsRNA, it cannot support the conclusion of obviousness drawn in the Office Action.

As noted above, Applicants have added new claims 98-101 herein. These claims recite dsRNA effector molecules selected from those having sequences set out in the specification as SEQ ID NOs 18-22. These sequences are demonstrated to be effective mediators of HBV expression inhibition in Example 1 of the specification.

In view of the above, Applicants submit that the proposed combination of Ill et al., Sallberg et al. and McCaffrey et al. fails to render the claimed invention obvious. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

In view of the above, all issues raised in the Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Should any other fees be associated with this submission, Applicants authorize the Commissioner to charge such fees to Nixon Peabody Deposit Account No. 50-0850, making reference to Docket No. 051058-034000. Any overpayments should also be credited to said Deposit Account.

Respectfully submitted,

Date: December 4, 2009

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